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INVITRO RELEASE COMPARISON OF NIFEDIPINE FROM MARKETED AND PREPARED CONTROLLED RELEASE FORMULATIONS BY MATHEMATICAL MODELING

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ABSTRACT

The objectives of this study were (a) To Perform *in-vitro* release study of marketed Nifedipine formulation,(b) To check effect of integrity on release profiles, (c) To determine the possibility of switchover from one formulation to another formulation and (d) To compare release profiles with formulated batches by application of mathematical models. Four marketed and two prepared controlled release (CR) products of Nifedipine were used in the study. Different release kinetic models were applied to drug release data in order to predict release mechanisms and kinetics. A criterion for choosing the most appropriate model was goodness of fit based on R^2, Akaike Information Criteria (AIC) and Model selection criteria (MSC). Marked differences in dissolution characteristics of preparations of halved tablets were observed as compare to intact tablets. Mathematical modeling and kinetics of drug release results depicted that the switchover from the product to other is not advisable for the dosage forms under study.

KEYWORDS: Dissolution, mathematical modeling, goodness of fit, Akaike Information Criteria and Model selection criteria.

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INTRODUCTION

Over the years, drug release from solid dosage forms has been the question of intense and profitable scientific developments. At any time when new solid dosage forms are developed, it is necessary to ensure that drug dissolution occurs in an appropriate and predictable manner. The pharmaceutical industry and the registration authorities do emphasis on drug dissolution studies. The quantitative analysis of the values obtained in dissolution is easier if mathematical formulae that express the dissolution results, as a function of some of the dosage form characteristics. In most of the cases the theoretical perception does not work and some empirical equations have shown to be more appropriate. Drug dissolution from solid dosage forms has been designated by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f(t). Some analytical explanations of the Q (t) function are commonly used, such as zero order, first order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, Korsmeyer-Peppas and Hopfenberg models. Other release parameters, such as dissolution time (tx%), assay time (tx min), dissolution efficiency (ED), difference factor (f1), similarity factor (f2) and Rescigno index have also been used to characterize drug dissolution/release profiles. A particular formulation may show different drug release profiles under different chemical environments and in different physical states owing to the nature of excipients and the method of manufacturing. Controlled release formulations are not the exceptions and therefore must be formulated in such a way that they remain independent of these variable factors, encountered most commonly when administered through per oral route in order to ensure a reliable in-vivo performance. Another most common practice is to split the dosage form. Though dividing a solid dosage form facilitate easy administration to the pediatric, geriatric or patients who have difficulty in swallowing [1], it may pose a serious risk in CR formulations where structural integrity plays an important role in controlling drug release pattern [2,3] and may result in faster drug release and lower blood levels [4]. In order to be divisiable, a CR: SR dosage form must not lose its controlled release characteristics upon division to avoid dose dumping.Most of the industries are engaged in manufacturing formulations containing drugs acting on CVS as the demand is increasing day-by-day. One of the prospective candidates from this category is Nifedipine - a calcium channel blocker - widely used for the treatment of angina pectoris and hypertension. Its frequent administration due to short biological half-life makes it a potential candidate for CR preparations and also needs special address regarding above discussed problems. [6]In present study, marketed and prepared Nifedipine formulations were compared for release kinetics applying mathematical models. The structural integrity and possibility for switchover the dosage forms was also scrutinized by the same mode.

MATERIALS AND METHODS

MATERIALS

Nifedipine was obtained as from SVKM's NMIMS, SPTM, Shirpur, India. Four Nifedipine (20 mg) CR F1, F2, F3 and F4; were purchased from local retail outlets. Two Nifedipine pelletized dosage form F5 and F6 were prepared in the lab. All the products were found to contain the labeled amounts of the drug when analyzed by the method described in Indian Pharmacopoeia.[4,5] Chemicals required for analysis such as hydrochloric acid, ingredients for phosphate buffer saline (disodium hydrogen phosphate, sodium chloride, potassium chloride, potassium dihydrogen phosphate) and methanol were procured from Qualigens Fine Chemicals, Mumbai and used as procured.

METHODS

CHARACTERIZATION OF NIFEDIPINE

Nifedipine's I.R spectrum was obtained using Perkin Elmer (Spectrum RX – 1) IR

Spectrometer. Wavelength Scan of solution of Nifedipine was recorded on a Perkin Elmer (Lambda – 25) U.V spectrometer. [4]

NIFEDIPINE CALIBRATION CURVES

Calibration curves of Nifedipine were prepared in different pH buffers (HCl pH 1.2, phosphate buffer pH 6.8) and methanol in the concentration range of 2.0–40 µg/ml. The drug was analyzed spectrophotometrically (Perkin Elmer lamda 25) at 238 nm.

IN-VITRO DISSOLUTION STUDIES

Dissolution studies with all the products were carried out according to USP <711>, at different pH levels (dissolution media volume 900 ml; for 2 hr in 0.1 N HCl followed by Phosphate Buffer 6.8 for remaining 6 hr) using paddle and rotating basket method at 150 rpm at 37 ± 0.5 ^{0} C temperature (Electrolab, TDT-08L, India). The samples were withdrawn periodically and replaced with fresh buffer and analyzed for Nifedipine spectrophotometrically at 238 nm. The detection method was found to be free from excipients interference by comparing the UV scans (200–400 nm) of different products with that of pure drug. In the studies with halved tablets, the tablets were weighed (Schimazdu, AUX 220) and then carefully cut at the middle using a sharp surgical blade. Their weights were checked prior to use. All products were observed visually for any physical changes taking place during the dissolution study. Final condition of the products, remaining after 8 hrs of experiment, was examined.

RELEASE MODELS

Various release kinetic models were used like zero-order, first-order, Higuchi model and Hixon-Crowell etc. Drug release data obtained was subjected to different models in order to establish the drug release mechanisms and kinetics. Criteria for choosing the most appropriate model was based on best goodness of fit, coefficient of determination (R^2), Model Selection Criteria (MSC) and Akaike Information Criteria (AIC).

RESULT AND DISCUSSION

Now-a-days, number of patients suffering from hypertension and angina are augmented due to contemporary life style. This triggered the demand of antihypertensive. Nifedipine is one of the major solution in this category, and available as alone & with different combinations. Nifedipine alone is safe and effective for the treatment. Due to this reason, there is a thirst in industry as well as in the market for the Nifedipine formulation. Due to scarcity of one product, the patient may switch over the other product which may lead to differences in bioavailability.

CHARACTERIZATION OF NIFEDIPINE

IR spectrum of Nifedipine (Figure no.1) depicted that the drug used was in pure form as indicated by stretching and bending compared with a standard IR spectrum of Nifedipine (Figure no.2). Wavelength scan of Nifedipine was recorded using the methanolic solution, peak was obtained at 238nm (Figure no 3). Calibration curves were plotted for Nifedipine in different buffers (Figure no. 4, 5, 6).

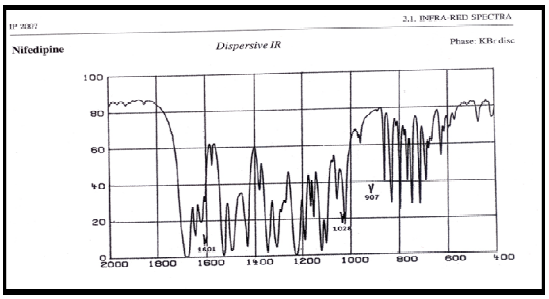

Figure 1
Nifedipine IR scan as per I.P

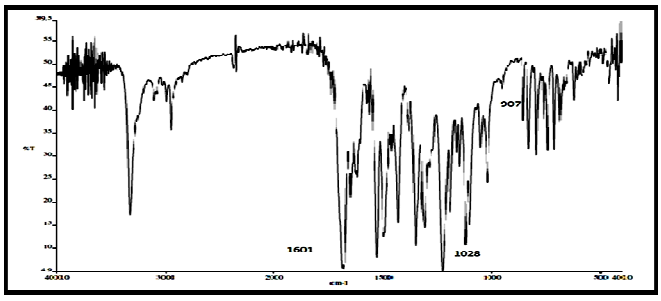

Figure 2
Nifedipine IR scan

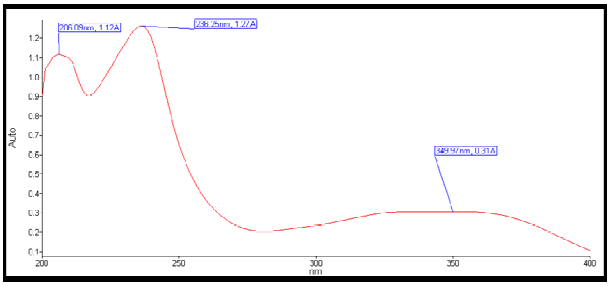

Figure 3
Nifedipine wavelength scan in methanol

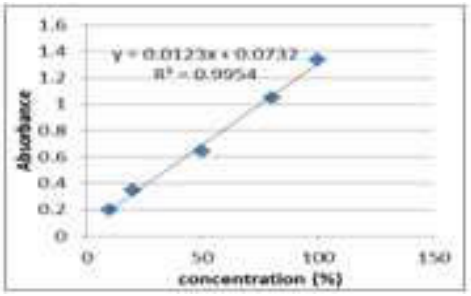

Figure4
Calibration curve of Methanol

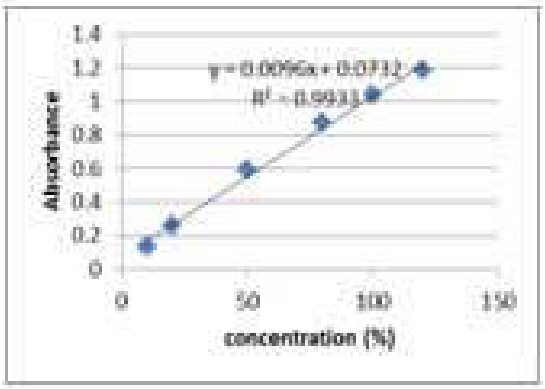

Figure 5
calibration curve of 0.1 N HCl

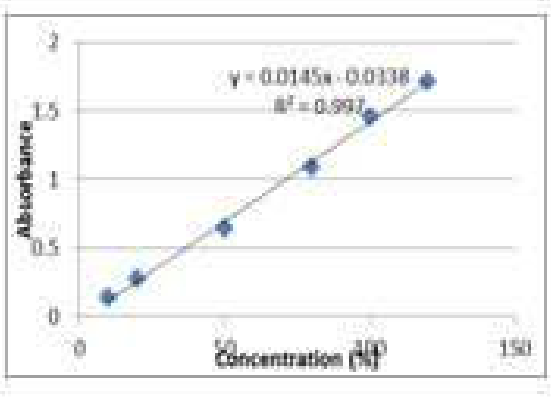

Figure 6
calibration curve of phosphate buffer 6.8

IN VITRO RELEASE AND EFFECT OF STRUCTURAL INTEGRITY

The dissolution data obtained from tablets and halved tablets (Products 'F1b', 'F2b', 'F3b') in pH 1.2 followed by pH 6.8 is shown in Table 1. The data from halved tablets was matched to that obtained from intact tablets in the same pH. The average dissolution data indicated that for 'F1', 'F2' and 'F3', in-vitro release of nifedipine was consistent with the intended sustained release tablets only when the tablets were intact. The split tablets showed an unfailingly higher release profile over time, reason attributed to this may be due to broken matrix structure of the tablets and increased surface area exposed to the dissolution media. Product 'F4', showed significant effect of integrity on total amount of drug released in halved as well as intact. For all four products, Relative standard deviation associated with the dissolution data of the split tablets was also higher than that of the intact tablets, which shows that the split tablets had higher variability as compared to the intact tablets.

Table No 1
Dissolution Release Data of marketed and prepared formulation

Time (Hrs.)	Formulation % Release (%RSD)								
	F1 a	F1 b	F2 a	F2 b	F3 a	F3 b	F4	F5	F6
1	17.8 (10.26)	26.24 (11.49)	17.65 (21.72)	39.70 (4.20)	22.94 (8.15)	24.03 (5.81)	49.34 (2.36)	9.91 (9.46)	0.73 (52.77)
2	30.53 (5.71)	35.89 (4.19)	27.64 (3.09)	42.32 (0.67)	32.11 (5.45)	34.44 (2.67)	56.72 (1.99)	12.42 (4.75)	3.51 (25.58)
4	83.19 (9.61)	94.83 (1.93)	83.22 (2.81)	99.42 (0.58)	71.38 (10.16)	80.73 (1.38)	-	27.73 (16.01)	10.49 (20.62)
6	91.52 (5.93)	97.33 (1.25)	94.7 (4.85)	71.82 (15.87)	76.68 (3.28)	85.74 (3.18)	-	34.34 (10.66)	13.89 (14.34)
8	84.02 (4.57)	89.38 (4.97)	-	-	79.96 (2.00)	88.1 (1.30)	-	40.36 (8.99)	15.93 (3.05)

RELEASE MODEL

In order to predict the kinetics of the drug release from the CR formulations various mathematical equations were used. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration.[8] The first order Eq. (2) describes the form of systems where release rate is concentration dependent.[9] Higuchi described the release from insoluble matrix as per a square root of time dependent process based on Fickian diffusion (Eq. (3)).[10] The Hixson–Crowell cube root law (Eq. (4)) describes the release from systems where there is a change in surface area and diameter of the particles or tablets.[11] The Korsmeyer – Peppas Eq. (5) describes the diffusional release mechanism from polymeric films.[12] Banker-Lonsdale Eq. (6) describes drug controlled release from the spherical matrix.[13] Hopfenberg Eq. (7) describes release of the drugs from surface eroding devices with several geometrics.[14, 15] The Gompertz Eq. (8) describes the comparison of release profile of drugs having good solubility and intermediate release rate.[16] Weibull Eq. (9) describes comparison of drug release profile of matrix type of drug delivery. [17, 18, 19, 20]

$$Q_t = Q_0 + K_0 t \quad \text{..... (1)}$$

$$\log C = \log C_0 - Kt / 2.303 \quad \text{..... (2)}$$

$$f = Q = \sqrt{D(2C - Cs)Cst} \quad \text{..... (3)}$$

$$w_o^{1/3} - w_t^{1/3} = \kappa t \quad \text{..... (4)}$$

$$M_t / M_\infty = kt^n \quad \text{..... (5)}$$

$$f1 = \frac{3}{2}\left[1 - \frac{\left(1 - \frac{Mt}{M\infty}\right)2}{3}\right]\frac{Mt}{M\infty} = kt \quad \text{..... (6)}$$

$$b \log (t - T_i) - \log a = \log [-\ln(1 - M)] \quad \text{..... (7)}$$

$$M_t / M_\infty = 1 - [1 - k_0 t / C_L a]^n \quad \text{..... (8)}$$

$$X(t) = X_{max} \exp [-\alpha e^{\beta \log t}] \quad \text{..... (9)}$$

DRUG RELEASE KINETICS

As shown in the Figure no.7, the curvilinear nature of the cumulative % drug released versus time plots suggest that none of the products follow zero order drug release kinetics which is confirmed by poor correlation coefficients, MSC and an AIC. Similar results were shown by Higuchian plots, for all the products. (Figure no.9)

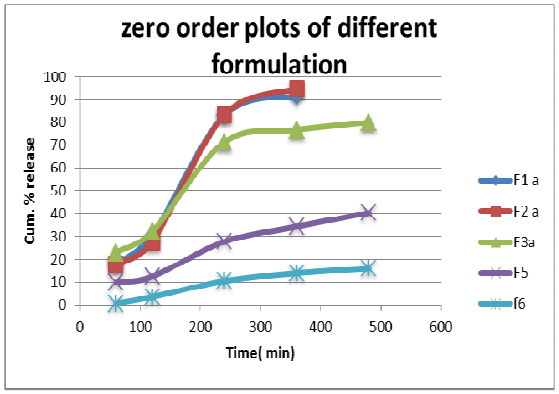

Figure 7
Zero order plots of different formulation

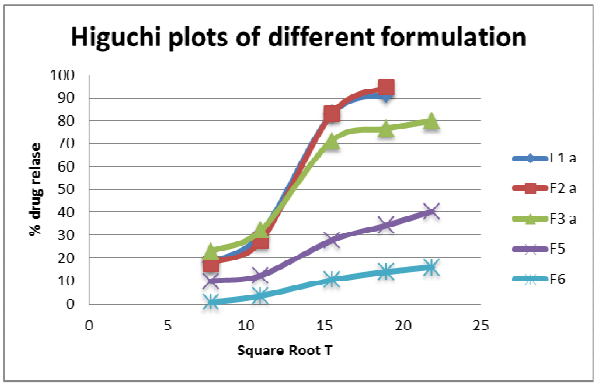

Figure 9
Higuchi plots of different formulations

The dissolution data of all the products was plotted in accordance with the first order equation. Figure no.8, depicted that a linear relationship was not obtained for 'F1a', 'F2a', 'F3a' , 'F5' and 'F6' indicating that the drug was embedded in the matrix and release was drug load independent. In accordance with Hixson–Crowell cube root law the dissolution data was also plotted (table no.2 & Figure no.10), results revealed that none of the product showed surface area change dependent or diameter change dependent release of the drug from the delivery systems.

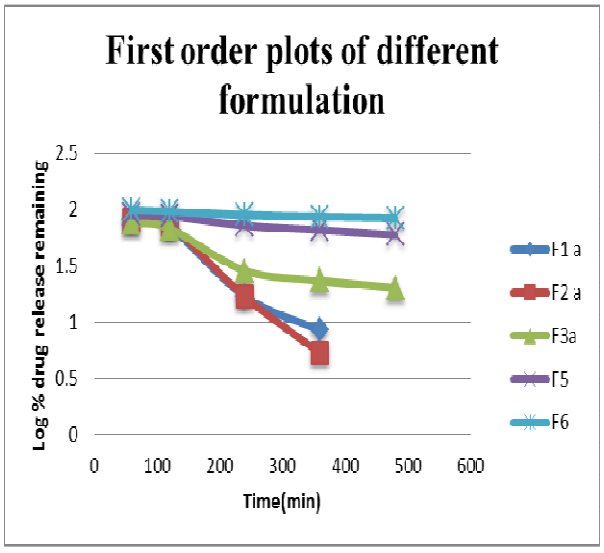

Figure 8
First Order plots of different formulation

Table no 2
Different Models and Its Parameters Related to different formulation.

Model	Parameter	F1 a *	F2 a*	F3 a*	F5	F6
Zero order	R^2	0.8923	0.9279	0.6525	0.9042	0.9490
	MSC	1.7280	2.1299	0.6570	1.9453	2.5760
	AIC	26.80	25.13	36.57	23.14	12.87
First order	R^2	0.8515	0.8500	0.9447	0.9615	0.9539
	MSC	1.4071	1.3969	2.4959	2.8559	2.6768
	AIC	28.08	28.07	27.38	18.59	12.37
Higuchi	R^2	0.8091	0.7709	0.8901	0.9106	0.7856
	MSC	1.1559	0.9737	1.8080	2.0150	1.1398
	AIC	29.09	29.76	30.82	22.79	20.05
Hixon-crowell	R^2	0.9088	0.9011	0.9162	0.9471	0.9527
	MSC	1.8946	1.8139	2.0791	2.5396	2.6504
	AIC	27.66	26.40	32.32	20.17	12.50
Korsmeyer-Peppas	R^2	0.9190	0.9308	0.9006	0.9766	0.9499
	MSC	1.5131	1.6709	1.5084	2.9562	2.1938
	AIC	26.13	26.97	29.46	18.09	14.78
Hopfenberg	R^2	0.9949	0.9894	0.9447	0.9614	0.9539
	MSC	4.2862	3.5504	2.0952	2.4548	2.2763
	AIC	16.56	19.45	29.38	20.59	14.37
Baker-Lonsdale	R^2	0.6967	0.6723	0.8492	0.8872	0.7765
	MSC	0.6931	0.6156	1.4920	1.7817	1.0983
	AIC	30.94	31.19	32.40	23.96	20.26
Weibull	R^2	0.9686	0.9751	0.9448	0.9801	0.9540
	MSC	2.4619	2.6932	2.0967	2.7171	2.2791
	AIC	23.86	22.88	29.37	19.28	14.36
Gompertz	R^2	0.8910	0.9310	0.9408	0.9741	0.9798
	MSC	1.2166	1.6742	2.0276	2.8540	3.1025
	AIC	28.84	26.96	29.72	18.60	10.24

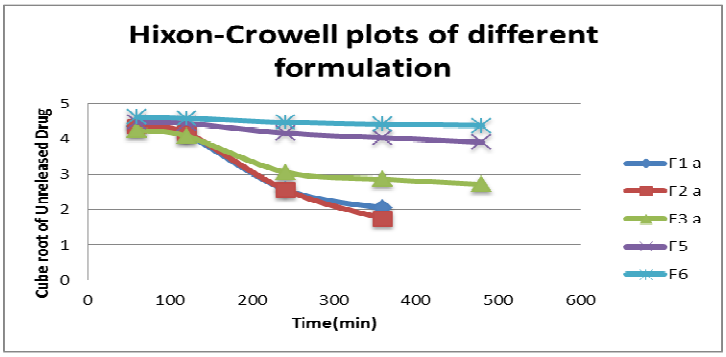

Figure 10
Hixon-Crowell plots of different formulations

As polymers forms the basis of controlled delivery systems, Korsmeyer-Peppas model was applied and as the formulations were of spherical type, Baker and Lonsdale model was applied to the dissolution data, non- linear plots were obtained for 'F1a', 'F2a', 'F3a' , 'F5' and 'F6'(Figure no.11). This indicates that the polymers used in formulation of delivery system do not release the drug by diffusion mechanism. It was also observed that formulation F1a and

F2a does not follow release pattern as per Fick's law of diffusion from matrix system but they showed that release of the drug based on surface erosion from the polymeric matrix as per Hopfenberg model. Formulation F3a and F5 showed that they did not follow release pattern as per surface erosion and bursting effect but they showed that release of the drug based on a matrix system as per Weibull model.

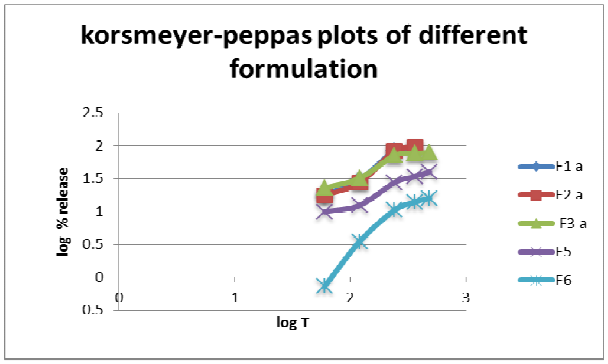

Figure 11
Korsmeyer-Peppas plots of different formulations

Dissolution data of halved tablets 'F1b', 'F2b' and 'F3b' in 0.1 N HCl followed by phosphate buffer 6.8 fit to different models nearly in the same way as that of individual intact tablets. Considering the determination coefficients (R^2), AIC and MSC, the models failed to fit to formulation F1a, F2a and F3a. The Hopfenberg model fitted to F1a and F2a. This indicates that the release kinetics for these formulations may be dependent on the surface erosion mechanism (table 3).

Table No 3
Best fit model and release pattern of different formulations

Sr . No.	Best fits models	Release pattern
F1 a	Hopfenberg	Erosion of device
F2 a	Hopfenberg	Erosion of device
F3 a	Weibull	Matrix system
F5	Weibull	Matrix system
F6	Gompertz	Intermediate release from matrix system

Study by Nirav Patel et. al,[21] showed that release pattern for oxcarbazepine CR tablets was surface erosion and diffusion matrix but the present study showed different release pattern the for F1a , F2a and F3a formulation, the reason behind this may be a type of polymer used in the formulation and its concentration in the formulation. Formulation F6 showed that it did not follow release pattern as per surface eroding and bursting effect. F.O. Costa et.al,(2003)[22] got intermediate release from matrix type system for Ibuprofen CR pellets but we got different release pattern the for pellet type dosage forms F5 and F6, the reason behind this may be geometry of formulation, type of polymer used in the formulation and its concentration in the formulation.

CONCLUSION

It is concluded from the study that pH of the dissolution media as well as structural integrity of dosage form play a significant role in describing the in-vitro drug release and predicted in-vivo performance of the CR dosage

formulations From the results, it can be inferred that in-vitro drug release process from all of the tested products is pH dependent and only one product showed pH independent release behavior. The products showed large brand to brand variations in the release patterns. Splitting of the tablets not only gave faster drug release, unlike the intended slower release profiles, but also increased the variability thereby reducing the reproducibility. Results suggest that it would be dangerous for a person to consume split the tablets. It can also be concluded that switchover from one formulation to other formulation is not advisable all the times as the release of API primarily depends on polymer used and various other formulation parameters which varies within manufacturers. Applications of mathematical models are helpful to determine release pattern of different marketed formulation. From the above result, it can be concluded that different polymer (in different marketed and formulated products) show different release pattern in specified concentration, so it will help in future for selection of polymer for particular release pattern.

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